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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/502,080

10/08/2004

J. Phillip Bowen

B40-002

3420

28156 7590 06/11/2009
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EXAMINER

GULLEDGE, BRIAN M

ART UNIT

PAPER NUMBER

1619

MAIL DATE

DELIVERY MODE

06/11/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/502,080	Applicant(s) BOWEN ET AL.	
	Examiner Brian Gulledge	Art Unit 1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 January 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 40-66 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 40-65 is/are rejected.
- 7) ☒ Claim(s) 66 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Note Regarding Last Action Mailed

The Examiner mailed a notice regarding a non-responsive amendment on May 15, 2009. The amendment received from the Applicant on January 30, 2009 was in fact proper, so the Applicant is advised to disregard the notice of non-responsive amendment. The statutory period to reply will begin with the mailing of this action.

Previous Rejections

Applicants' arguments, filed January 30, 2009, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40-48, 50-55, and 57-65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of some forms of cancer with solenopsin A, does not reasonably provide enablement for treatment of some forms of cancer with a reasonably representative genus of *trans*-2,6-disubstituted piperidine

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compounds generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by “undue experimentation,” the Federal Circuit has stated:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).¹

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

- 1) the quantity of experimentation necessary,
- 2) the amount of direction or guidance provided,
- 3) the presence or absence of working examples,
- 4) the nature of the invention,
- 5) the state of the prior art,
- 6) the relative skill of those in the art,
- 7) the predictability of the art, and
- 8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA

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1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

The nature of the invention, state and predictability of the art, and relative skill level:

The invention relates to a method of treating cancer comprising the administration of a therapeutically effective amount of a *trans*-2,6-disubstituted piperidine compound. The relative skill of those in the art is high, that of an M.D. or Ph.D. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites Arbisar et al. (*Blood*, **2007**, 109(2), pages 560-565). Arbisar et al. discloses compounds that are of the same general formula as instantly recited (page 562, figure 1). Arbisar et al. discloses that only one single compound, solenopsin A, significantly impaired SVR proliferation (page 561, last full paragraph). Moreover, the compounds tested had substantial homology to their structure – all the tested compounds had R¹ as methyl, and hydrocarbon side-chains for R². Thus, Arbisar et al. suggests that minor structural changes (such as shortening the hydrocarbon side-chain) can lead to significant changes in activity.

The breadth of the claims: The claims encompass treatment of cancer with *trans*-2,6-disubstituted piperidine compounds (substituted with hydrocarbons), and are not limited to just solenopsin A.

The amount of direction or guidance provided and the presence or absence of working examples: The specification provides no direction or guidance for practicing the claimed invention in its “full scope”. No reasonably specific guidance is provided concerning useful compounds, other than solenopsin A, that are demonstrated to inhibit cell mediated angiogenesis.

¹ As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is “undue”, not

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The latter is corroborated by the working examples. The instant disclosure provides no evidence to suggest that the activity of this compound can be extrapolated to all the other compounds disclosed that have different hydrocarbon substituents, and thus does not meet the “how to use” prong of 35 USC 112, first paragraph with regard thereto.

The quantity of experimentation necessary: Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed *trans*-2,6-disubstituted piperidine compounds could be predictably used to treat cancers as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the claimed invention in its “full scope” a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claims 40-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating some forms of cancer, including solid tumor based cancers such as breast, prostate, ovarian, gastric, skin, colon, and lung, does not reasonably provide enablement for treatment of cancer in general or the treatment of oral cancer, non-solid tumor cancers, or cutaneous malignancies generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re*

“experimentation”.

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Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by “undue experimentation,” the Federal Circuit has stated:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

- 1) the quantity of experimentation necessary,
- 2) the amount of direction or guidance provided,
- 3) the presence or absence of working examples,
- 4) the nature of the invention,
- 5) the state of the prior art,
- 6) the relative skill of those in the art,
- 7) the predictability of the art, and
- 8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

The nature of the invention, state and predictability of the art, and relative skill level:

The invention relates to a method of treating cancer comprising the administration of a therapeutically effective amount of a *trans*-2,6-disubstituted piperidine compound. The relative skill of those in the art is high, that of an M.D. or Ph.D. That factor is outweighed, however, by

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the unpredictable nature of the art. Solenopsin A has been shown by Arbisar et al. (*Blood*, **2007**, *109*(2), pages 560-565) to have activity in a particular assay (the SVR angiogenesis assay), and have some structural and property homology with the phospholipid ethers miltefosine and perifosine (page 564, fifth full paragraph). This assay and these phospholipid ethers have demonstrated activity for treating breast, prostate, ovarian, and gastric cancers (Kondapaka et al., *Mol. Cancer Ther.*, **2003**, *2*, pages 1093-1103; page 1094, first partial paragraph) and lung cancer (Gills et al., *Mol. Cancer Ther.*, **2006**, *5*, pages 713-722; page 1094, abstract).

However, as demonstrated by other references, such as Calabresi et al. (Goodman & Gilman, 10th Edition, McGraw Hill, **2001**, pages 1381-1385), the art is not predictable. Calabresi et al. discloses chemotherapeutic agents useful in treating neoplastic diseases (page 1381). The teachings of Calabresi et al. demonstrate that specific compounds as well as general classes of drug are useful only for a subset of types of cancer. For example, the pyrimidine analog fluoruracil can be used to treat breast, colon, and ovarian cancer, but not granulocytic or lymphocytic leukemias, whereas another pyrimidine analog, cytarabine, is useful for treating granulocytic and lymphocytic leukemias, but not breast, colon, or ovarian cancer (page 1382, table IX-I). Another example is that anti-angiogenesis agents are known to not be effective against oral cancer, as taught by Gleich et al. (*Anticancer Research*, **1998**, *18*(4A), pages 2607-2609) (abstract). Knowling et al. (*Invest. New Drugs*, **2006**, *24*, pages 435-439) teaches that soft tissue sarcoma is not responsive to anti-angiogenic agents (abstract). And Sosman et al. (*Clin. Cancer Res.*, **2006**, *12*(7), pages 2376s-2383s) teaches that it is unlikely that application of an angiogenesis inhibitor is unlikely to have any substantial impact on treating melanoma (abstract), a form of cutaneous malignancy.

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The breadth of the claims: The claims encompass treatment of all types cancers. Included are breast, prostate, ovarian, and gastric cancers, as well as leukemias, oral cancer, and melanoma

The amount of direction or guidance provided and the presence or absence of working examples: The specification provides no direction or guidance for practicing the claimed invention in its “full scope”. No reasonably specific guidance is provided concerning useful therapeutic protocols for treating cancers, other than that the compounds inhibit cell mediated angiogenesis. The latter is corroborated by the working examples. The instant disclosure provides no evidence to suggest that this activity can be extrapolated to treating the recited forms of cancer generally and thus does not meet the “how to use” prong of 35 USC 112, first paragraph with regard thereto.

The quantity of experimentation necessary: Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used to treat cancers such as oral cancer, leukemias, and melanomas as well as breast, prostate, ovarian, and gastric cancers as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the claimed invention in its “full scope” a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

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Claims Free of Prior Art

The pending claims (40-66) are free of the prior art. The elected species, where R¹ is methyl and R² is undecyl, is not known for use in treating any form of cancer. The compound was known prior to this application, and has been used to treat parasitic infections (US Patent 4,910,209) and to suppress fire ants (6,369,078), but has not been linked cancer treatment.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Gulledge whose telephone number is (571) 270-5756. The examiner can normally be reached on Monday-Thursday 6:00am - 3:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BMG

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612